FIG. 1

(-) Phenylahistin
1
Pd/C, H2
r.1., 2h
3
Pd/C, H2
r.1., 24h
5
(+) Phenylahistin
2
Pd/C, H2
r.1., 2h
4
Pd/C, H2
r.1., 24h
6

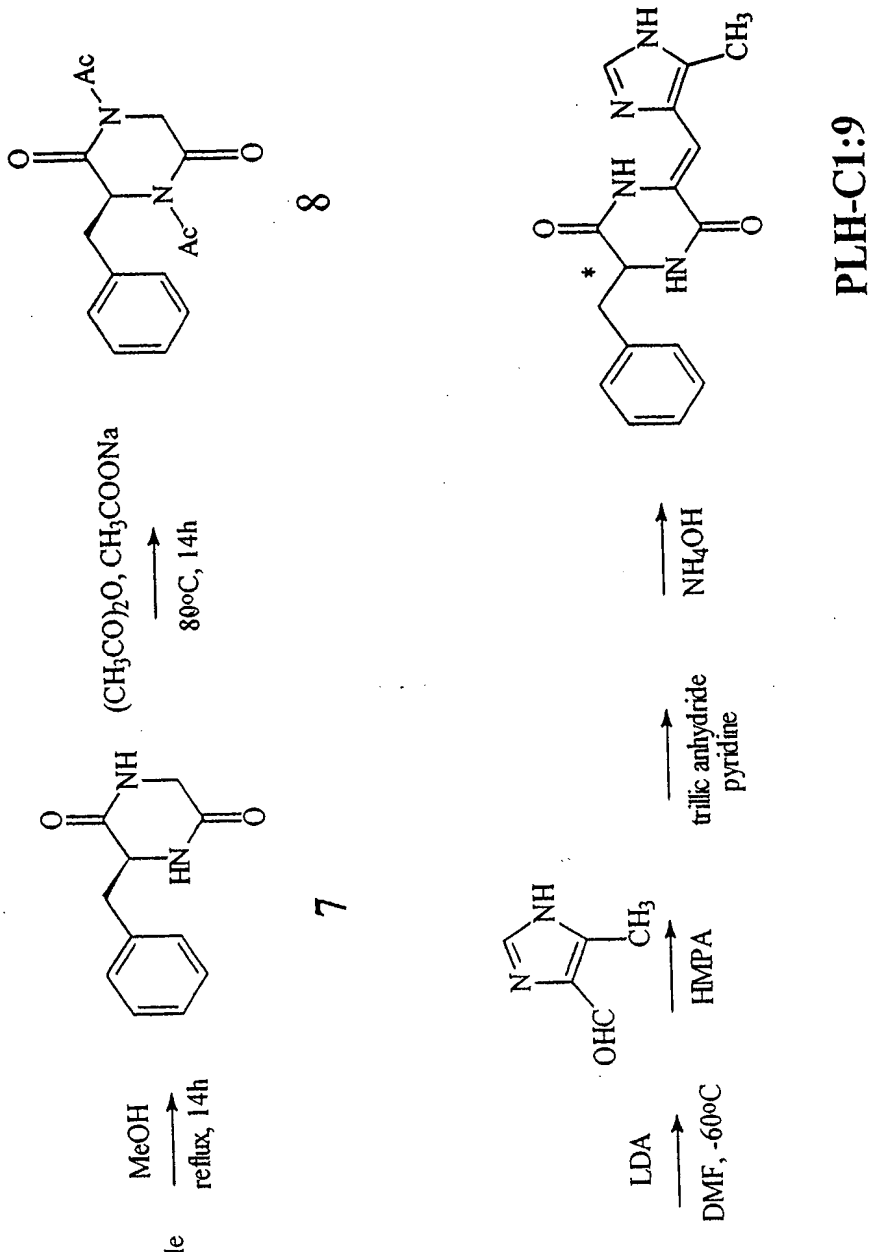

H2N-Phe-Gly-OMe
MeOH
reflux, 14h
7
(CH3CO)2O, CH3COONa
80°C, 14h
8
LDA
DMF, -60°C
HMPA
trillic anhydride
pyridine
NH4OH
PLH-C1:9

FIG. 2

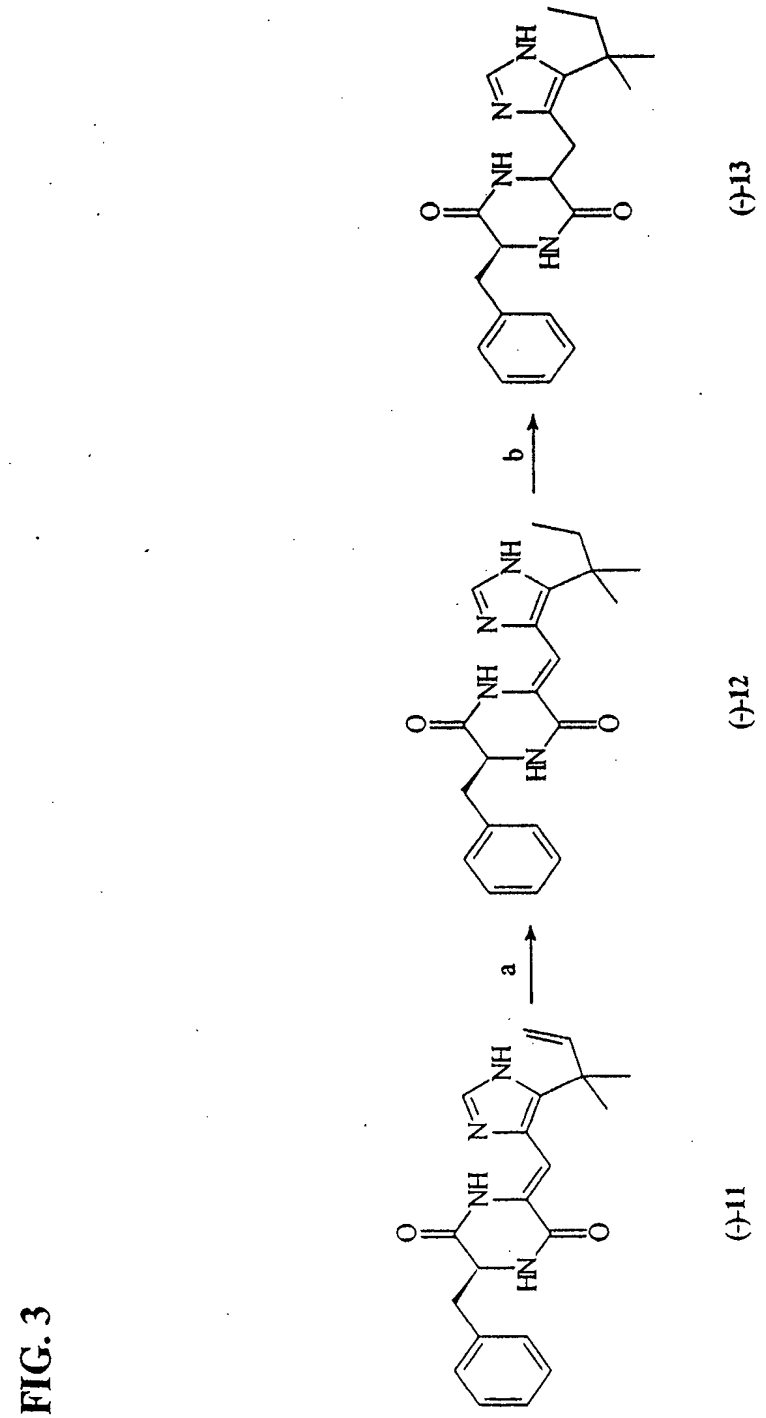


FIG. 3

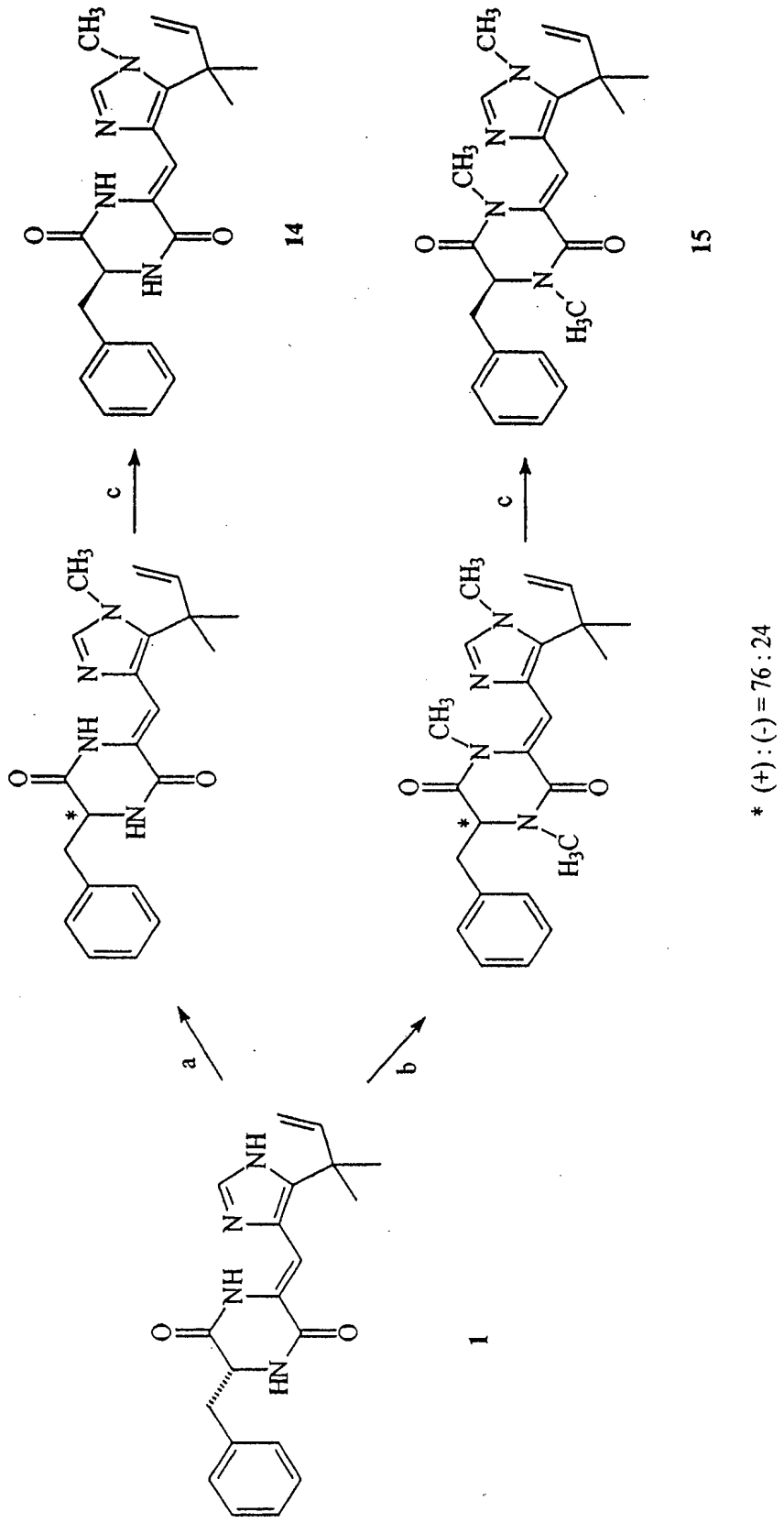
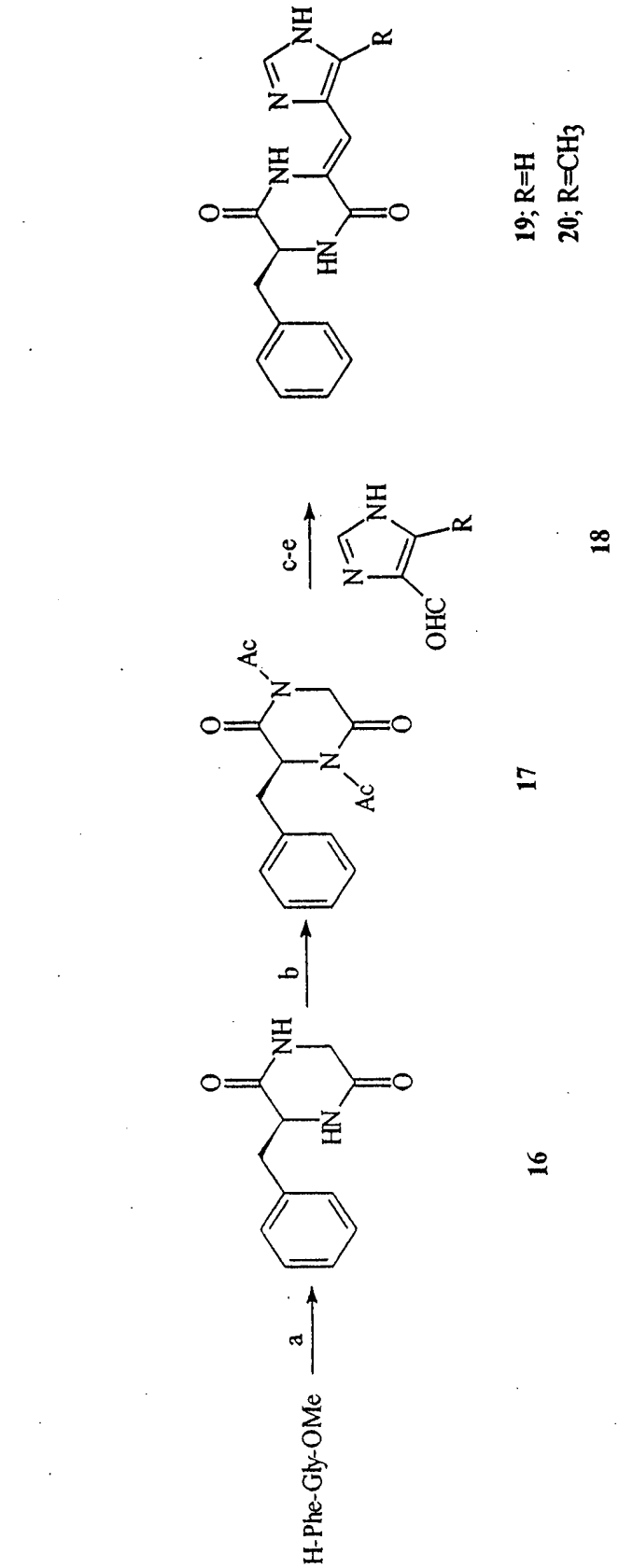


FIG. 4

FIG. 5



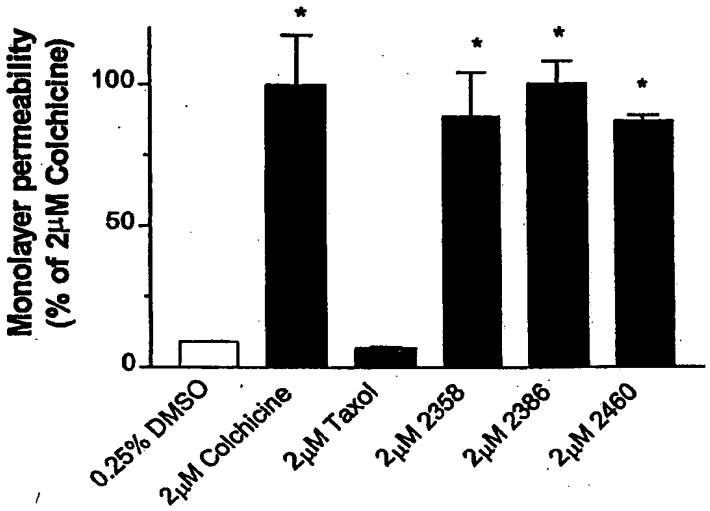

Monolayer permeability
(% of 2μM Colchicine)
100
50
0
*
*
*
*
0.25% DMSO
2μM Colchicine
2μM Taxol
2μM 2358
2μM 2386
2μM 2460

FIG. 6

A

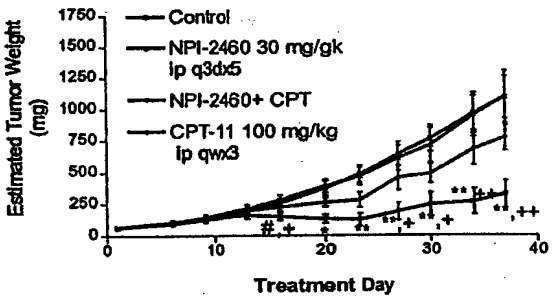

Estimated Tumor Weight (mg)
1750
1500
1250
1000
750
500
250
0
0
10
20
30
40
Treatment Day
Control
NPI-2460 30 mg/gk ip q3dx5
NPI-2460+ CPT
CPT-11 100 mg/kg ip qwx3

FIG. 7

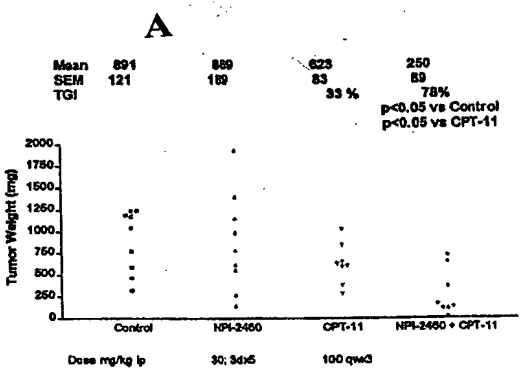
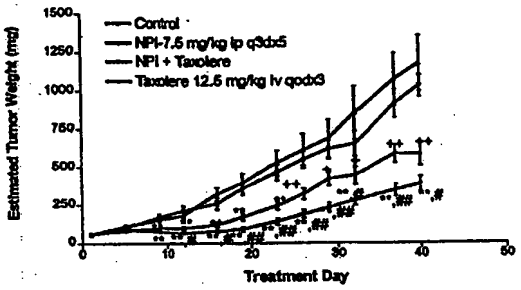

A
Mean 891 889 623 250
SEM 121 189 83 89
TGI 33 % 78%
p<0.05 vs Control
p<0.05 vs CPT-11
Tumor Weight (mg)
2000
1750
1500
1250
1000
750
500
250
0
Control
NPI-2460
CPT-11
NPI-2460 + CPT-11
Dose mg/kg ip
30; 3dx5
100 qwx3

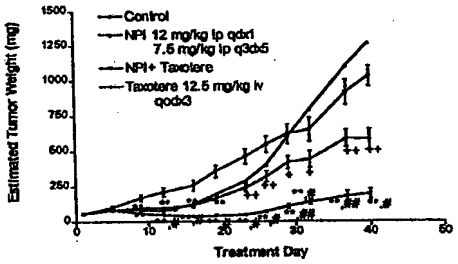
FIG. 8

A.



* p< 0.05 vs Control ANOVA
** p<0.01 vs Control ANOVA
\+ p<0.05 vs Control t-test
++ p<0.01 vs Control t-test
\# p<0.05 vs Taxotere t-test
p<0.01 vs Taxotere t-test

B.



Day 12 -> n=1 for NPI-2366 Alone

C.

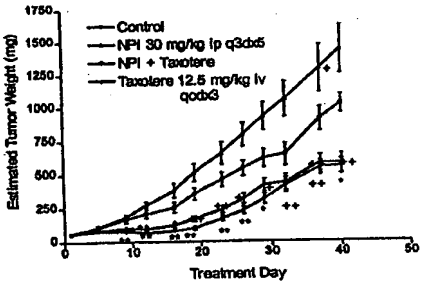


FIG. 9

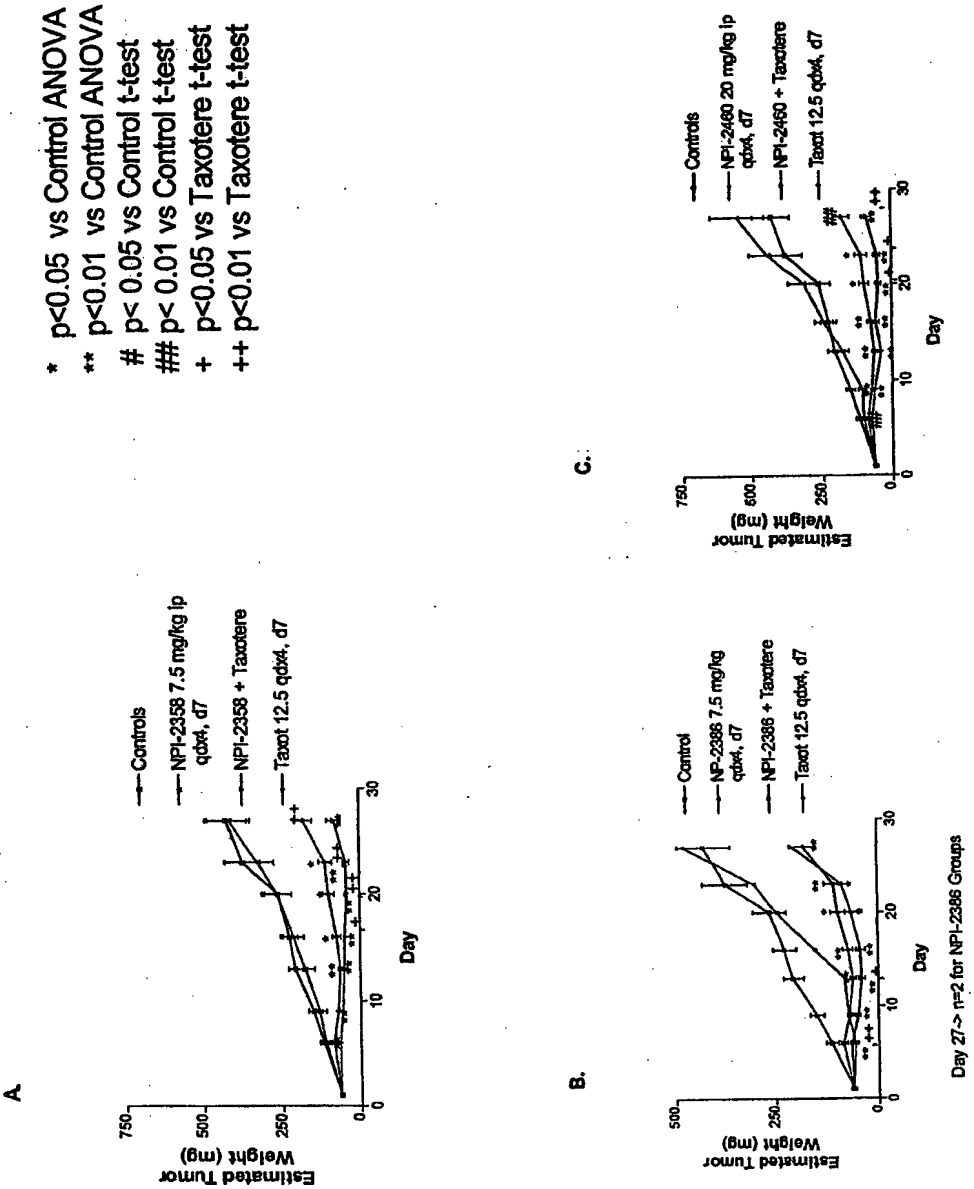

* p<0.05 vs Control ANOVA
** p<0.01 vs Control ANOVA
# p< 0.05 vs Control t-test
p< 0.01 vs Control t-test
+ p<0.05 vs Taxotere t-test
++ p<0.01 vs Taxotere t-test
A.
Controls
NPI-2358 7.5 mg/kg ip qdx4, d7
NPI-2358 + Taxotere
Taxot 12.5 qdx4, d7
Estimated Tumor Weight (mg)
Day
B.
Control
NP-2386 7.5 mg/kg qdx4, d7
NPI-2386 + Taxotere
Taxot 12.5 qdx4, d7
Estimated Tumor Weight (mg)
Day
Day 27-> n=2 for NPI-2386 Groups
C.
Controls
NPI-2460 20 mg/kg ip qdx4, d7
NPI-2460 + Taxotere
Taxot 12.5 qdx4, d7
Estimated Tumor Weight (mg)
Day

FIG. 10

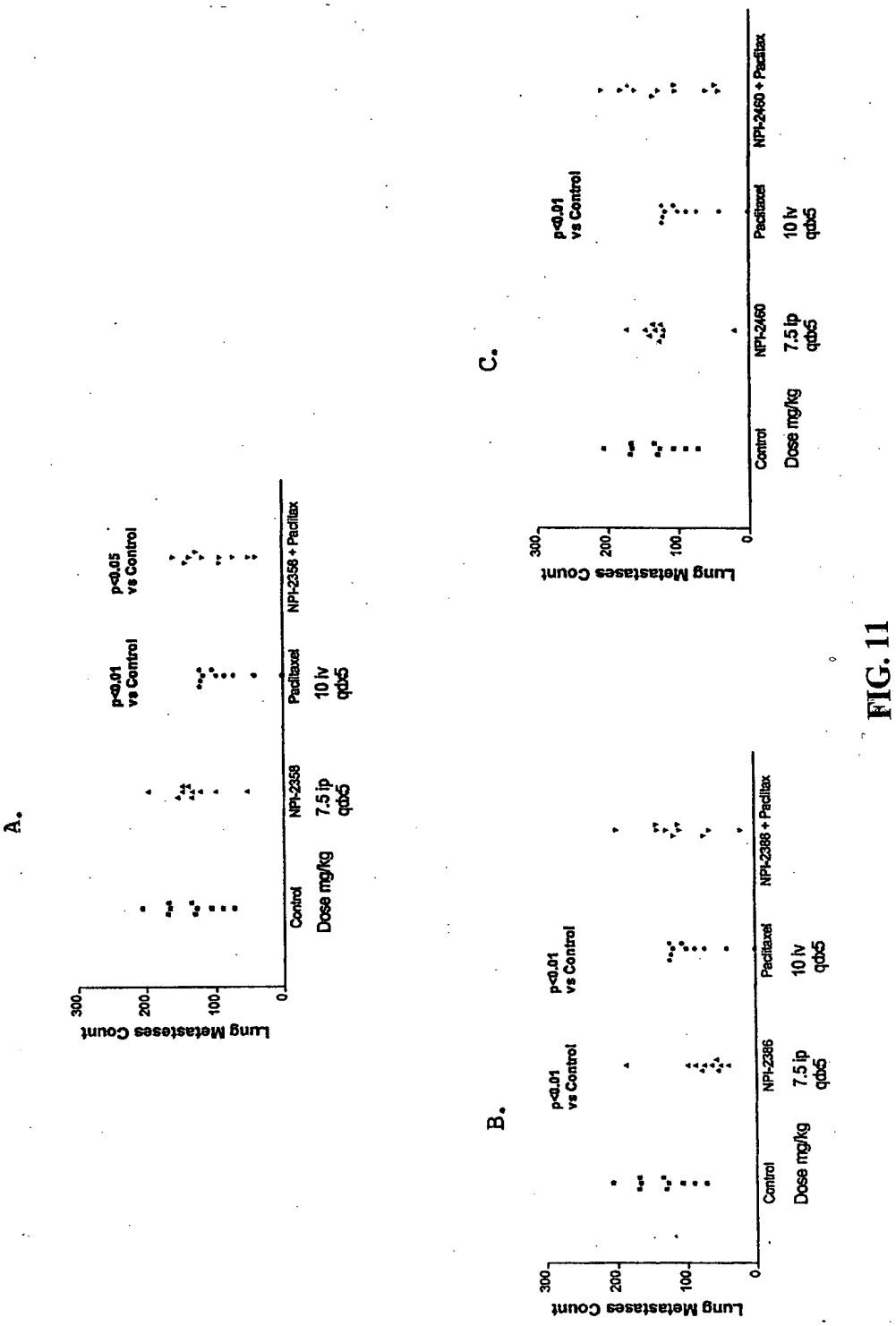

A.
Lung Metastases Count
300
200
100
0
p<0.01 vs Control
p<0.05 vs Control
Control
NPI-2358
Paclitaxel
NPI-2358 + Paclitax
Dose mg/kg
7.5 ip qd5
10 iv qd5
B.
Lung Metastases Count
300
200
100
0
p<0.01 vs Control
p<0.01 vs Control
Control
NPI-2386
Paclitaxel
NPI-2386 + Paclitax
Dose mg/kg
7.5 ip qd5
10 iv qd5
C.
Lung Metastases Count
300
200
100
0
p<0.01 vs Control
Control
NPI-2460
Paclitaxel
NPI-2460 + Paclitax
Dose mg/kg
7.5 ip qd5
10 iv qd5

FIG. 11